European Journal of Pediatrics
https://doi.org/10.1007/s00431-021-04318-2

ORIGINAL ARTICLE

Follow-up practices for children and adolescents with celiac disease: results of an international survey

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Received: 4 June 2021 / Revised: 8 November 2021 / Accepted: 9 November 2021

Abstract

Adequate follow-up in celiac disease is important to improve dietary compliance and treat disease-related symptoms and possible complications. However, data on the follow-up of celiac children is scarce. We aimed to assess current pediatric celiac follow-up practices across Europe. Pediatricians and pediatric gastroenterologists from 35 countries in Europe, Israel, Turkey, and Russia completed an anonymous survey which comprised a 52-item questionnaire developed by the ESPGHAN Special Interest Group on Celiac Disease. A total of 911 physicians, the majority of whom exclusively worked in pediatric care (83%) and academic institutions (60%), completed the questionnaire. Mean age and mean experience with celiac care were 48.7 years (±10.6) and 15.7 years (±9.9), respectively. The vast majority (≥92%) always assessed anthropometry, dietary adherence, and tissue-transglutaminase IgA-antibodies at every visit, with the first visit being between 3 and 6 months after diagnosis. Other parameters (% always tested) were as follows: complete blood count (60%), iron status (48%), liver enzymes (42%), thyroid function (38%), and vitamin D (26%). Quality of life was never assessed by 35% of the responding physicians. Transition to adult care was mostly completed via a written transition report (37%) or no formal transition at all (27%).

Conclusions: Follow-up of celiac children and adolescents in Europe may be improved, especially regarding a more rational use of (laboratory) tests, dietary and QoL assessment, and transition to adult care. Evidence-based advice from international scientific societies is needed.

What is Known:
- *Follow-up in celiac disease is important to treat disease-related symptoms, improve dietary compliance, and prevent possible complications.*
- *There is a lack of consensus about the appropriate follow-up.*

What is New:
- *Almost all European physicians assess anthropometry, tissue-transglutaminase IgA-antibodies, and dietary adherence at every visit, but there are large variations in other follow-up aspects.*
- *Follow-up could be improved by a more rational use of (laboratory) tests, increased intention to dietary compliance, and quality of life together with transition programs to adult care.*

Keywords Celiac disease · Children and adolescents · Follow-up · Inquiry · European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)

Margreet Wessels and Jernej Dolinsek contributed equally to this paper.

Communicated by Peter de Winter.

On behalf of the ESPGHAN Special Interest Group on Celiac Disease, https://www.espghan.org/our-organisation/council-and-committees/gastroenterology-committee#Working%20Groups_Special%20Interest%20Groups

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Abbreviations

AGA	Anti-gliadin antibodies
BMD	Bone mineral density
CBC	Complete blood count
CD	Celiac disease
DGPA	Deamidated gliadin peptide antibodies
EMA	Endomysial antibodies

Published online: 24 November 2021

ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition
ESPGHAN SIG-CD	ESPGHAN Special Interest Group on CD
GFD	Gluten-free diet
GIP	Gluten immunogenic peptides
QoL	Quality of life
TGA	Tissue-transglutaminase antibodies
TSH	Thyroid stimulating hormone
USA	United States of America

Introduction

The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) is responsible for the most cited evidence-based guidelines for the diagnosis of celiac disease (CD) [1, 2]. Once diagnosed, CD can be successfully treated with a lifelong gluten-free diet (GFD) which restores small bowel histology and improves symptoms [3]. However, this diet is difficult to follow and may lead to social constraints, with noncompliance varying from 25 to 50% among children and adolescents, as well as occasional nutritionally imbalanced diets [4, 5]. The need for effective long-term follow-up to support the dietary compliance, treat disease-related symptoms and possible complications has been acknowledged by many expert groups [3]. Therefore, guidance for the long-term follow-up and management of children and adolescents with CD is necessary. At present, standard medical care for CD children consists of visits to the pediatrician or pediatric gastroenterologist to evaluate overall health, anthropometrics, GFD adherence, and laboratory investigations to rule out deficiencies, and co-morbidity. In 2016, evidence-informed expert recommendations were published for the management of pediatric CD by pediatric gastroenterologists from the United States of America (USA) and Canada [6], in which the shortage of good quality data regarding this matter was emphasized. However, no recommendations have been published at the European level. In addition, the recommendations on follow-up from the USA and Canada may not apply or be followed in Europe. The experience of the members of the ESPGHAN Special Interest Group on CD (ESPGHAN SIG-CD) indicates that there is a lack of consensus about the appropriate follow-up intervals for children and adolescents with CD, which laboratory or other tests should be used, including novel methods and possibilities such as measuring gluten immunogenic peptides (GIP) in urine or in feces, the use of self-assessment tools, including point of care tests, and the use of e-Health [7, 8]. There is furthermore no consensus on follow-up and management of adolescents with CD, an age group with a well-known poor compliance with the diet, or the special needs of CD patients with associated diseases, such as type 1 diabetes or Down's syndrome. Follow-up during transition to adulthood is a special cause of concern, since the majority of celiac patients between 20 and 40 years of age diagnosed during childhood currently receive no medical or dietary supervision [9]. For these reasons, the ESPGHAN SIG-CD decided to conduct a survey among as many European pediatricians and pediatric gastroenterologists as possible to get information on the current follow-up practices for children and adolescents with CD in Europe.

Methods

For the data collection, a special web-based form that included questions regarding the follow-up and management of CD was designed. The set of questions was developed by the ESPGHAN SIG-CD, after adaptation of the questionnaire designed for the "Focus IN CD project" (https://www.interreg-central.eu/Content.Node/Focus-IN-CD.html). The final English version included 52 open-ended and multiple-choice questions.

The web-based platform SurveyMonkey was used to upload the questionnaire. Without preselection, pediatric gastroenterologists and pediatricians were encouraged to participate via local and international networks, including the ESPGHAN website, the members of the ESPGHAN SIG-CD, and their national PGHAN societies.

The study was conducted between the beginning of December 2019 and the end of March 2020. Altogether, 1082 physicians completed the questionnaire. Inclusion criteria for further analysis consisted of respondents from European countries, Israel, Turkey, and Russia, working in pediatric or combined pediatric and adult care. Respondents reporting to be involved in the regular follow-up but not the diagnosis of CD patients were not excluded from the analysis. Answers from a total of 911 physicians from 35 countries were analyzed after excluding those from physicians who did not follow CD patients ($N=126$), exclusively working in adult care centers ($N=29$) and practicing outside of Europe, Israel, Turkey, and Russia ($N=16$). The highest number of physicians who fulfilled the inclusion criteria came from Italy (16%), Spain (16%), Israel (13%), and the United Kingdom (10%) (Fig. 1).

The answers to our survey were analyzed according to the number of CD patients diagnosed and followed annually, the type of institution of the physician (academic/non-academic and pediatric/combined pediatric and adult care), ESPGHAN membership (yes/no), and professional experience (0–5 years; 6–10 years; 11–20 years; > 20 years).

The analysis was performed using IBM SPSS Statistics 22.0 for Windows. Statistical analysis was performed by

means of chi-square tests, with p-values < 0.05 considered statistically significant.

Results

Responder characteristics are shown in Table 1. Mean age and mean experience with celiac care were 48.7 years (±10.6) and 15.7 years (±9.9), respectively. The majority followed the "no-biopsy" ESPGHAN diagnostic approach, as advised at the time of the inquiry for certain patients [2]. Those who diagnosed fewer CD patients per year (1–10 patients) or had less patients in follow-up (1–50 patients) adhered significantly less to the ESPGHAN diagnostic guidelines (both $p < 0.001$).

The first follow-up visit was reported to be scheduled < 3 months by 57% and between 4 and 6 months by 40% of respondents. Only 3.5% of the respondents scheduled the first visit after 6 months after diagnosis. After the first follow-up visit, the planning of subsequent visits depended on the resolution of symptoms. If absent, 84% scheduled the next appointment after 4–6 months. Without established improvement, 73% reported to schedule the next follow-up visit within 3 months. Subsequently, the majority (88%) of physicians scheduled the next appointment after > 6 months. More than half of physicians (65%) increased the number of visits during adolescence, independent of the type of institution or their professional experience.

As shown in Table 2, more than 90% of the physicians always assess growth, tissue-transglutaminase antibodies (TGA), and diet adherence during follow-up. Non-ESPGHAN members assessed weight and height and TGA significantly less frequent compared to ESPGHAN members (weight: 3% versus 0.5%, $p = 0.025$; height: 5% versus 1%, $p = 0.017$; TGA 91% versus 96%, $p = 0.034$). The latter was also true for physicians working in combined pediatric-adult care (88% versus 93%, $p = 0.029$). Substantial variation was reported on the use of endomysial (EMA), deamidated gliadin peptide (DGPA), and anti-gliadin (AGA) antibodies (Table 2). EMA assessment was not related to any responder characteristics. Point-of-care tests for TGA and GIP assessment in urine or in stool were never used by the majority of physicians (96% and 97%, respectively), with no differences observed between respondents.

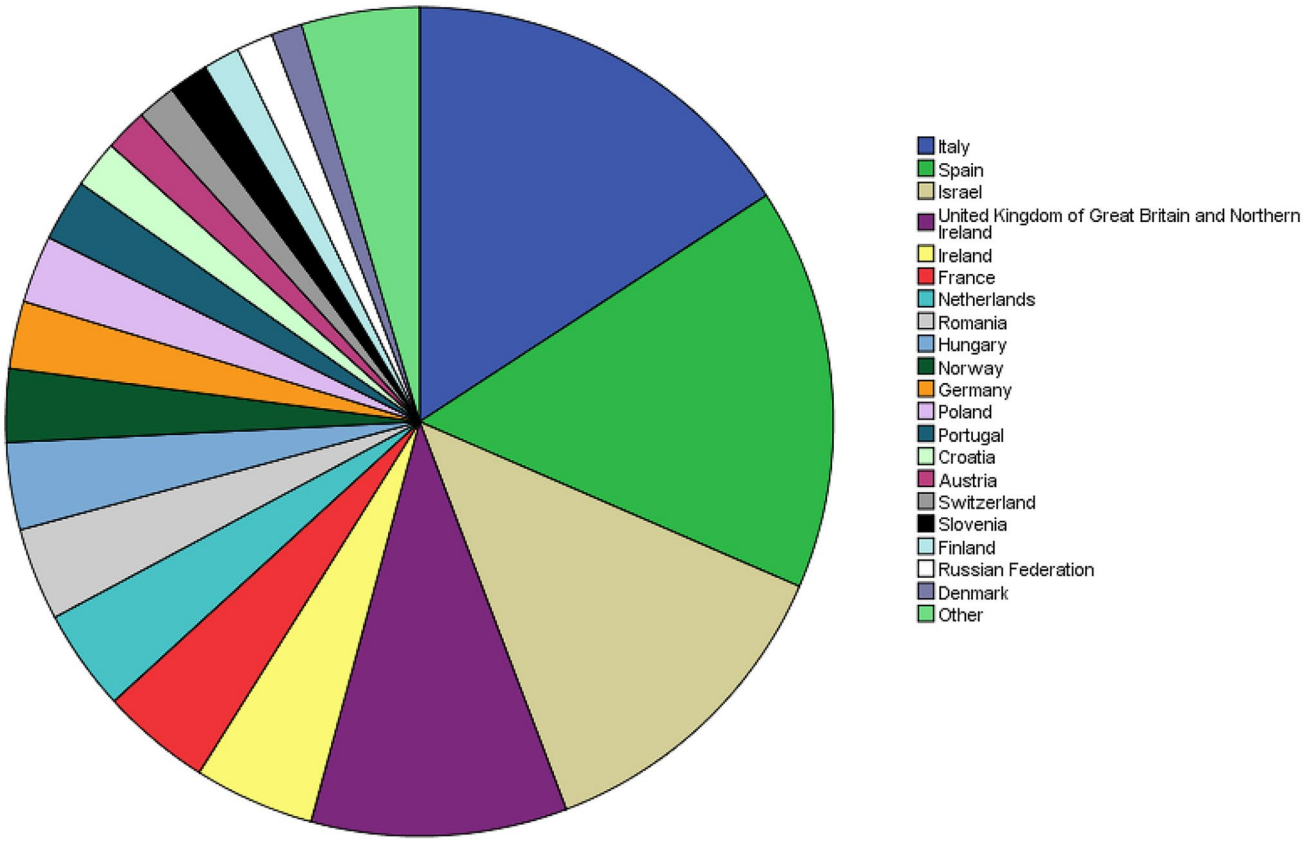

Fig. 1 Countries of origin of the 911 physicians responding to the inquiry on the follow-up of celiac disease in children and adolescents. Others: Armenia, Belgium, Bosnia and Herzegovina, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Latvia, Lithuania, Montenegro, Serbia, Sweden, The former Yugoslav Republic of Macedonia, and Turkey

Table 1 Characteristics of the 911 physicians responding to the inquiry on the follow-up of celiac disease in children and adolescents

Characteristics	Percentage
Field of practice	
- Pediatric care	83
- Combined pediatric-adult care	17
Practice setting	
- Non-academic	40
- Academic	60
ESPGHAN membership	
- Yes	25
- No	75
Years of experience	
- 0–5 yrs	18
- 6–10 yrs	21
- 11–20 yrs	35
- > 20 yrs	26
Number of celiac patients diagnosed each year	
- None	3
- 1–10	45
- 11–30	33
- 31–50	10
- > 50	9
Number of celiac patients in follow-up	
- 1–50	43
- 51–100	18
- 101–200	19
- 201–500	14
- > 500	6
Gender	
- Female	63
Use of the no-biopsy approach in children/adolescents to diagnose celiac disease according to the ESPGHAN criteria*	
- Yes, in all patients	13
- Yes, in some patients	77
- No	10

*ESPGHAN 2012 criteria valid at the time of the inquiry [1]

Additional tests were performed with varying frequency (Table 2). Only the assessment of thyroid function was related to responders' characteristics since it was done significantly more often by physicians working in combined pediatric-adult care compared to pediatric care (always assessed by 56% versus 35%, $p = 0.003$), by those diagnosing > 50 patients per year (always assessed by 51% versus 30%, $p = 0.012$) and by those following > 500 patients (50% versus 30%) (p-values < 0.001).

The majority of physicians (85%) reported always performing family screening when a new CD patient is diagnosed.

Three quarters of the physicians reported to have specialist dietetic counseling available at their institution, with a significantly higher availability reported by physicians working in academic institutions (78% versus 71%, $p = 0.04$) and those following > 500 patients (86%, $p = 0.04$). During follow-up, 16% of the respondents reported not to refer patients to a dietitian whereas 20% referred all of their patients during follow-up. Referral was significantly influenced by reimbursement, with less referrals occurring when patients/parents had to fully finance dietetic counseling themselves compared to those receiving full financial coverage from a third party (3% versus 51%; $p < 0.01$). Methods used to assess dietary adherence were anamnesis (32%), 24-h diet recall or evaluation by a dietitian (23%), a combined anamnesis or 24-h diet recall/dietetic evaluation with CD-specific serology (resp. 21% and 3%), the Biagi score (a short GFD questionnaire [10]) (4%), and CD-specific serology alone (11%).

General psychology services were reported to be available by 75% of the respondents, with 2.5% having CD-focused psychology. Moreover, these services were more commonly available in academic institutions (83% versus 69% respectively; $p < 0.001$). Referral to a psychologist during follow-up was not routine practice for 95% of the respondents, and 35% of them never assessed quality of life (QoL) (Table 2). Those who did used anamnesis and QoL-related questionnaires such as CD-QOL, CDDUX, and PEDS-QL [11–13].

Transition to adult care occurred in 65% of cases at the age of 18 years, in 30% before 18 years of age, and in 5% after 18 years of age. Written transition report (37%) or no formal transition at all (27%) were most commonly reported. Only 4% of the respondents either had a special transition clinic or used a specific transition protocol. ESPGHAN members reported special transition clinics (7% versus 3%; $p = 0.004$), specific transition protocols (7% versus 3%; $p = 0.006$), and written transition report (56% versus 31%; $p < 0.001$) more often than non-members.

Discussion

Our results of the largest inquiry on follow-up thus far provide insight into the current health care for celiac children throughout Europe and identify gaps that may be improved upon in the future.

In the absence of evidence-based European follow-up recommendations, both similarities and discrepancies regarding follow-up of children with CD were reported among the large group of consulted physicians from different parts of Europe. Among the similarities were the standard assessment of anthropometry, TGA, and dietary adherence at every visit. Similarities were also reported on the timing of the follow-up visits and screening of first-degree relatives of a new diagnosed celiac case.

Table 2 Assessments performed during follow-up visits as reported by 911 physicians to the enquiry on the follow-up of celiac disease in children and adolescents

	Number of responses	Always (%)	Sometimes (%)	Never (%)
Anthropometrics				
Weight	755	98	2	0
Height	754	96	4	0
Assessment of				
Dietary adherence	740	92	5	3
Quality of life	744	32	33	35
Celiac-specific serology				
Tissue-transglutaminase antibodies (TGA)	695	93	6	1
Endomysial antibodies	671	21	46	33
Deamidated gliadin peptide antibodies	624	9	41	50
Anti-gliadin antibodies	624	5	17	78
TGA point of care test	631	1	3	96
Additional laboratory tests				
Complete blood count	605	60	39	1
Iron count	602	48	51	1
Liver tests	603	42	54	3
Thyroid function test	599	38	60	2
Vitamin D	598	26	69	5
GIP in urine/stool	631	1	2	97
Hepatitis B vaccination status	591	4	41	55
Bone mineral density	596	4	70	26
Intestinal biopsies	605	1	57	42
Prescription of supplements				
Vitamine D	673	20	71	9
Iron	674	2	88	10
Calcium	669	2	72	26
Multivitamins	671	5	58	38
Prescription of probiotics	667	2	41	57
Family screening	652	85	14	1

On the other hand, this survey shows large variations in other aspects, such as the laboratory tests used. Half of the physicians reported performing structural analysis of CBC and iron status, and more than a third performed thyroid screening at every follow-up visit, while others did not or did so only occasionally.

As many children have deficiencies of iron, folate, and vitamin B12 at CD diagnosis, which usually normalizes 1 year after treatment with a GFD [7, 14, 15], assessment should be performed from diagnosis until normalization, but may not be necessary in compliant, asymptomatic children [7]. An increased risk of thyroid disease in children with CD on a GFD has been reported in several studies [16–19], hence, the recommendation to screen thyroid function during follow-up [6]. This policy may perhaps be questionable, however, as elevated levels of thyroid stimulating hormone (TSH) are found in 5–19% of CD patients without abnormal levels of Free Thyroxine 4 [7]. Thus, these assessments may represent a diagnostic excess leading to more anxiety and costs than necessary.

Vitamin D levels have been shown to be low both at diagnosis and during follow-up, albeit comparable to the general pediatric population [7]. As such, if indicated, vitamin D testing and supplementing can, therefore, be considered good clinical care. With regard to bone mineral density (BMD), it is well known that CD patients may present with reduced BMD at diagnosis [20, 21], without clinical predictors of low BMD at diagnosis presently available [22]. Even though regular BMD measurements in celiac children on a GFD do not seem necessary [23], 4% and 70% of the physicians always and occasionally assessed BMD during follow-up, respectively, a possibly unnecessary and not cost-effective policy.

More than 90% of the responding physicians reported to assess dietary compliance during follow-up with substantial variation. Our results indicate a preference for anamnesis, evaluation by a dietitian or a 24-h recall. Some physicians combined these methods with CD-specific serology. Few reported to use serology as the only tool. However,

anamnesis, self-reported dietary adherence and serology have been reported to oversee important dietary transgressions [7, 24–26], indicating that dietary adherence is best assessed by a face-to-face consultation with the dietician or by comparable standardized questionnaires, in combination with determination of specific-CD antibodies [7].

Relatively, new tests such as point-of-care tests for TGA and GIP assessment in urine or in stool were hardly used by the responding physicians. However, given that these are a novel topic of interest and research, this may change in the future.

The pattern of follow-up visits was quite similar among the physicians and mostly in line with existing publications regarding the first follow-up visit scheduled 3–6 months after diagnosis, followed, in case of stability, by annual visits [27, 28]. Similar results were found in a recent study performed in a select number of Central European countries [29]. Dietary transgressions tend to occur more often in adolescents due to stigmatization, feelings of isolation in social situations, and absence of complaints after gluten ingestion in some teenagers [30]. In line with this, more than half of the physicians reported to increase the frequency of visits during adolescence. However, the opposite was found in several countries of Central Europe, where the majority of physicians did not increase the frequency [29].

Despite the fact that QoL of children and adolescents with CD is often low [31], 35% of the physicians reported to never assess QoL during follow-up. The physicians who did used a large variation of instruments, from simply asking the patient (approximately 50%) to asking the patient to complete various QoL questionnaires such as CD-QOL, CDDUX, and PEDS-QL [11–13] (31%). Physicians seldomly reported to refer their patients to the psychologist, even though psychological counseling has been shown to play an important role in reducing potential psychosocial stress associated with the GFD [32, 33]. Different mental health disorders and psychological symptoms have been reported in association with CD, suggesting the need for psychological assessment of selected CD patients in order to improve their quality of life [34].

Transition to adult care, a period with a possible negative impact on dietary adherence and QoL [35], may be improved as almost one-third of the physicians reported not having formal transition strategies in their institution. This is in agreement with recent data showing that the transition of care for young adults with CD is inconsistent, particularly among asymptomatic patients [36]. For these reasons, a structured transition of care, including written information on diagnosis, comorbidities, and dietary compliance has been recommended earlier [9].

The strengths of our study are the large number of participating physicians from a variety of European countries providing data from daily clinical practice. Physicians were both academic and non-academic pediatricians, with various ages and working experience, as well as varying numbers of celiac patients in care both at diagnosis and follow-up. These participants can, therefore, be considered as representative for the general pediatric health care providers for children and adolescents with CD in Europe. On the other hand, one possible weakness is the overrepresentation of physicians from certain, relatively large countries, such as Italy, Spain, Israel, and the UK. However, the results of our inquiry are complementary to the results found in Central European Countries [29] which together, represent a broad reflection of the day-to-day approach in which European physicians care for children with CD.

In conclusion, the answers from the inquiry describe the actual situation regarding follow-up of pediatric celiac disease in European countries. They indicate that the follow-up of children and adolescents with CD in Europe may be improved, especially with regard to a more rational use of (laboratory) tests, assessment of the dietary compliance, CD-specific QoL, and transition to adult care. In light of the identified knowledge gaps, the ESPGHAN SIG-CD is gathering the available evidence about how the follow-up should be organized and preparing a position paper on the management of pediatric CD in order to improve the quality of care for celiac children and adolescents.

Authors' contributions Margreet Wessels, Gemma Castillejo, Jernej Dolinsek, and Luisa Mearin designed the study; Margreet Wessels, Gemma Castillejo, Jernej Dolinsek, Ester Donat, Maria Roca, Francesco Valitutti, and Luisa Mearin developed the 52-item questionnaire and organized distribution across Europe; Margreet Wessels, Jernej Dolinsek, Petra Riznik, and Anne Veenvliet analyzed the data; Margreet Wessels, Jernej Dolinsek, and Luisa Mearin wrote the paper; Luisa Mearin has the primary responsibility for the final content. All the authors have read and approved the final manuscript.

Availability of data and material Available as SPSS file on request.

Code availability N/A.

Declarations

Ethical approval N/A.

Consent to participate N/A.

Consent for publication All the authors have read the manuscript and support the submission and publication if accepted.

Conflict of interest The authors declare no competing interests.

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